REMARKS

Applicants have amended paragraph [0124] of the specification to include the following language:

> Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules.

This language is taken from Rudnic *et al.*, Chapter 89 of *Remington's Pharmaceutical Sciences*, 18th Ed., pages 1658 and 1662, copies of which were previously submitted as Exhibit 1. Applicants maintain that no new matter was added in the amendment of ¶[0124] which was incorporated by reference in ¶[0176] of the specification, as Applicants are permitted to add the actual text of material incorporated by reference:

> The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. *M.P.E.P. §2163.07(b)* (emphasis added).

The amendment of paragraph [0124] is again submitted for the Examiner's consideration because the pending Office Action states that "the amendment to paragraph [0124] has not been entered." *Office Action* at 5.

Applicants have amended claims 30, 41 and 42 to recite administration in a single dosage form. Support for this amendment can be found, for example, in original claim 20. Claims 40, 43 and 50 are amended to clarify the claims. Support for new claim 57 can be found, for example, at original claim 3. Support for new claim 58 can be found, for example, at ¶[0012], [0016], and [0040]. For the reasons discussed below, Applicants respectfully traverse the rejections of the pending Office Action.

Objection to Amendment of the Specification

The Examiner has objected under 35 U.S.C. § 132(a) to the previously submitted amendment to ¶[0124] of the specification, which is again presented herein, "because it introduces new matter into the disclosure." *Office Action* at 2. The Examiner states that "[i]t is acknowledged that Applicants have incorporated by reference the source for the new text," but that the insertion of the text into the specification is improper because "the amendment constitutes addition of essential subject matter which may only be incorporated by reference to a U.S. patent or patent application publication." *Office Action* at 2-4. The Examiner relies on 37 C.F.R. § 1.57(c) and (d), and M.P.E.P. § 608.01(p) to support his objection. Applicants respectfully traverse the objection.

Without acquiescing to the Examiner's assertion that the amended subject matter is "essential matter," Applicants respectfully submit that the Examiner is mistaken regarding whether Applicants may amend the specification to include essential subject matter previously incorporated by reference to a non-patent reference. While it is true that under 37 C.F.R. § 1.57(c) "essential material" may be incorporated by reference only to a U.S. patent or U.S. patent publication, 37 C.F.R. § 1.57(g) states:

> An incorporation of material by reference that does not comply with paragraphs (b), (c), or (d) of this section is not effective to incorporate such material unless corrected within any time period set by the Office, but in no case later than the close of prosecution as defined by § 1.114(b), or abandonment of the application, whichever occurs earlier." *37 C.F.R. § 1.57(g)* (emphasis added).

In addition, the M.P.E.P. § 608.01(p), cited by the Examiner, clearly states that non-compliance with 37 C.F.R. § 1.57(c) can be corrected by amending the specification to include the essential matter previously incorporated by reference:

> **2. Improper Incorporation**
>
> 37 CFR 1.57(f) addresses corrections of incorporation by reference by inserting the material previously incorporated by reference. A noncompliant incorporation by reference statement may be corrected by an amendment. 37 CFR 1.57(f). However, the amendment must not include new matter. Incorporating by reference material that was not incorporated by reference on filing of an application may introduce new matter. An incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c). The improper incorporation by reference is not effective to incorporate the material unless corrected by the

> applicant (37 CFR 1.57(g)). Any underlying objection or rejection (e.g., under 35 U.S.C. 112) should be made by the examiner **until** applicant corrects the improper incorporation by reference by submitting an amendment to amend the specification or drawings to include the material incorporated by reference. *M.P.E.P. § 608.01(p)* (emphasis added).

In addition, Applicants direct the Examiner's attention to Example 2 of M.P.E.P. § 608.01(p), where the applicant adds a claim limitation that is supported only by a foreign patent that is incorporated by reference. The M.P.E.P. states that rejection of the amendment under 35 U.S.C. § 112, first paragraph, is proper, but that the applicant can overcome the rejection "by filing an amendment under 37 CFR 1.57(f) to add the subject material disclosed in the foreign patent into the specification." *M.P.E.P. § 608.01(p)* (emphasis added).

Based on the above, it is clear that even if Applicants' amendment of ¶[0124] of the instant specification added "essential matter," the amendment was proper and allowable under 37 C.F.R. § 1.57(f) and (g). Therefore, Applicants respectfully request that the objection to the amendment of ¶[0124] of the specification be withdrawn.

35 U.S.C. § 112, First Paragraph, Written Description and Enablement

The Examiner has rejected claims 30-56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, asserting that the claims contain new matter.

First, the Examiner asserts that the limitation in claims 48 and 54 that the capsule is a single compartment capsule constitutes new matter. The Examiner states that "the amendment to paragraph [0124] was not entered," and that "neither explicit, implicit nor inherent support for a 'single compartment capsule'" was found in the version of paragraph [0124] prior to the amendment, or anywhere else in the specification. *Office Action* at 6. Applicants respectfully traverse.

As Applicants have previously stated, it is clear from the version of paragraph [0124] prior to the amendment that there is adequate written description support the single compartment limitation of claims 48 and 54. However, to make explicit that that Applicants contemplated customary capsules having a shell (typically made of gelatin) enclosing a single compartment containing the pharmaceutical formulation of active compound(s) and carriers and/or excipients, Applicants have amended paragraph [0124] of the specification.

This amendment to the specification is proper for the reasons discussed above. When combined with the statement in paragraph [0124] that multicompartment capsules were further contemplated, it would be more than clear to one of skill in the art that at the time of filing Applicants were in possession of the invention as claimed in pending claims 48 and 54. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection of claims 48 and 54 over the recitation of the phrase "single compartment capsule."

The Examiner also rejects claims 30, 40, 43, 50 and 56 for reciting a claimed method wherein the pharmaceutical formulation is prepared by preparing a first population of carrier particles, preparing a second population of carrier particles, and combining the first and second populations of carrier particles in a unit dosage form. The Examiner asserts that the specification does not provide support for this limitation. *Office Action* at 6-7. Applicants respectfully traverse.

Applicants respectfully submit that the Examiner is applying an impermissibly strict "*in haec verba*" requirement. The proper test for satisfaction of the written description requirement is "[w]hether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1562-63, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991) (citations omitted). Applicants remind the Examiner that "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims," – conclusory statements are not sufficient. *M.P.E.P. §2163.*

Applicants respectfully submit that one of skill in the art would clearly recognize that at the time of filing, Applicants' were in possession of the invention as now claimed. Applicants have previously pointed the Examiner's attention to ¶[0017] of the specification as filed. The relevant portion states:

> [0017] The first and second populations of carrier particles may be formulated separately or, preferably, incorporated into the same pharmaceutical formulation. In a preferred embodiment, the drug and bioadhesive compound are formulated into tablets or multiparticulate formulations (e.g., microparticles, miniparticles, minitablets). In preferred embodiments, the penetration enhancer is formulated into a tablet, multiparticulate, emulsion, microemulsion or self-emulsifying

> system. The two types of carrier particles are **then** formulated separately or together into oral dosage formulations such as tablets, capsules or gelcaps in a manner that does not impair the adhesive or release properties of the other. *Specification* at ¶[0017] (emphasis added).

As ¶[0017] indicates, in a preferred embodiment the two populations of carrier particles are formulated separately into tablets, or multiparticulate formulations and "are then formulated separately or together" into oral dosage formulations. Clearly, the separate formulation of the two populations of carrier particles occurs first, and then they can be combined into a dosage formulation such as a tablet.

The fact that Applicants contemplated and were in possession of the claimed invention at the time of filing is also supported by the disclosure in ¶[0040]:

> [0040] In a preferred embodiment, the second population of carrier particles (comprising the penetration enhancer) further comprise an enteric delayed release coating or matrix to delay dissolution until reaching a location in the intestine downstream from where the drug and penetration enhancer are released from the first population of carrier particles which do not comprise a delayed release coating or matrix. This delayed release coating or matrix is different from, or has a different thickness than, the delayed release coating or matrix on the pharmaceutical formulation (e.g. capsule or tablet) described above which causes release of the penetration enhancer after the combination of drug and penetration enhancer is released from the first population of carrier particles. *Specification* at ¶[0040].

One of skill in the art will recognize from the description of this embodiment that to formulate a capsule or tablet comprising two distinct populations of carrier particles, one population of which has an enteric or delayed release coating and the other population does not, it is necessary to separately formulate the two populations of carrier particles, and then bring them together to form the capsule or tablet.

This disclosure clearly supports the claim language rejected by the Examiner. It is the Examiner's burden to explain why one of skill in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In the absence of any such explanation, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 30, 40, 43, 50 and 56 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description support.

Finally, the Examiner has also rejected the claims as lacking enablement, stating that "since a disclosure cannot teach one to make or use something that has not been described." *Office Action* at 7. For at least the above reasons, Applicants submit that the pending claims are adequately described, and therefore request that the Examiner withdraw the enablement rejection of claims 30-56 as well.

35 U.S.C. § 103(a) – Obviousness

The Examiner rejects claims 30, 33 and 37 under 35 U.S.C. § 103(a) as obvious over McKay (US 5,877,309) in view of Chen (US 5,508,040) and Bai (5,840,329). The Examiner argues that McKay discloses oligonucleotide formulations comprising many of the recited components of the pending claims. *Office Action* at 8. However, the Examiner admits that McKay "does not particularly teach that the formulation is made such that the first and second populations of carriers are arranged such that intestinal tissue is activated by the penetration enhancer prior to arrival of the drug..." *Id.* To overcome this deficiency in McKay, the Examiner relies on Chen and Bai, arguing that "it was well recognized in the art at the time the invention was made that controlled release formulations can provide timed release of therapeutic agents." *Id.*

In addition, the Examiner rejects claims 30, 33 and 37 under 35 U.S.C. § 103(a) as obvious over McKay (US 5,877,309) in view of Chen (US 5,508,040) Bai (5,840,329) and Bennett (US 5,514,788). The Examiner states that McKay, Chan and Bai do not disclose SEQ ID NO:1, but Bennett does. *Office Action* at 10. Applicants respectfully traverse.

Failure to Establish a Prima Facie Case of Obviousness

It is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability..." *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). To establish a *prima facie* case of obviousness, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Merely establishing that the claimed elements can be found in the prior art is not sufficient to establish a *prima facie* case of obviousness:

> As is clear from cases such as *Adams,* a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was,

> independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added).

Instead, the Court made it clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007) (citations omitted).

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for the reasons detailed below.

Applicants submit that the Examiner has failed to articulate any reason why one of skill in the art would modify the formulation of McKay based on Bai, and Chen to arrive at the claimed formulations of independent claims 30, 40 and 56. The Examiner's entire rationale is a single conclusory statement: "One of ordinary skill in the art would have been motivated to combine the references to create [the] claimed invention because McKay does not particularly teach how to make the formulation for delivery of the oligonucleotide to the intestines, while Chan [*sic*] and Bai provide more specific guidance on making pulsatile releasing formulations." *Office Action* at 9. Applicants respectfully submit that this statement is not sufficient to support a *prima facie* case of obviousness.

The Examiner's rationale begs the question of why one would be motivated to combine the references to arrive at the claimed invention by arguing that that the reason to combine the references is to make the invention. Essentially, the Examiner argues that because McKay does not teach how to provide enhanced intestinal absorption of a drug, one of skill in the art would look to the teachings of Chen and Bai and make Applicants' invention. This is insufficient to establish a *prima facie* case of obviousness.

The Examiner is required to explain how, out of the hundreds of possible pulsed release, delayed release, sequential release, etc. formulations that could be derived from the teachings of McKay, Chen and Bai, one of skill in the art would arrive at the particular formulation

Applicants have claimed. Applicants can not find any teaching in McKay, Chen or Bai that suggest combining bioadhesives and drug in one population of carrier particles to retain the drug at a first location in the intestine, while using a second population of particles containing penetration enhancer to activate intestinal tissue prior to arrival of the drug, and thus improve intestinal absorption of the drug.

As previously explained, it is believed that the administration of a formulation comprising two distinct populations of carrier particles provides the claimed methods with an advantage that is not found in the cited references. First, by preparing a first population of carrier particles comprising a drug and a bioadhesive, "the drug will acquire some degree of adhesive properties which will extend its residence time and, consequently, absorptive potential, over the region of intestinal mucosa made permeable by penetration enhancers." *Specification* at ¶[0015]. In addition, by having a separate population of carrier particles comprising penetration enhancers, it is believed that a further advantage is gained:

> ... Upon dissolution in the intestine, the penetration enhancers are released and move down the intestine while acting on the mucosal membrane. Concurrently, the drug-bioadhesive component adheres to the mucosal membrane and releases drug both directly to the penetration enhancer-activated mucosal membrane and into the lumenal solution from where it can also be absorbed. In this manner, tissue will be activated prior to the arrival of the drug which will transit through a maximum area of activated tissue, minimizing the possibility of any drug transiting ahead of the penetration enhancer and consequently through unactivated tissue where it could not be absorbed. *Specification* at ¶[0016] (emphasis added).

None of the cited references provide a rationale or guidance that would lead one of skill in the art to Applicants' formulation. In the absence of such a rationale, the Examiner has failed to establish a *prima facie* case of obviousness.

In addition to failing to articulate any rationale for modifying the cited references, Applicants submit that the cited references, alone or in combination, do not teach or suggest all of the limitations of the presently pending claims. For example, claim 30 recites in part, a first population of carrier particles comprising a drug, a carrier particle-forming substance and a bioadhesive material; and a second population of carrier particles comprising a penetration enhancer, wherein the two populations are formulated individually and then combined. The Examiner has not indicated where in the references these elements can be found.

Finally, Applicants submit that the Examiner has not established that there is a reasonable expectation of success. As stated above, the Examiner does not offer any evidence or reasoning to suggest that some or all of the numerous formulations disclosed by McKay, Bai and Chen would result in a formulation for enhanced intestinal absorption of a drug.

In sum, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least these reasons. Applicants therefore request reconsideration and withdraw of the rejection of the pending claims under 35 U.S.C. § 103(a) over the cited references.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications of Assignee

Applicants wish to draw the Examiner's attention to the following patent(s) or application(s) of the present application's assignee. Applicants encourage the Examiner to review and monitor the prosecution of the following patent(s) and/or application(s) throughout the pendency of this application.

Patent or Serial Number	**Title**	**Issued/Filed**
09/944,493	PULSATILE RELEASE COMPOSITIONS AND METHODS FOR ENHANCED INTESTINAL DRUG ABSORPTION	08/22/2001

11/000,814	PULSATILE RELEASE COMPOSITIONS AND METHODS FOR ENHANCED GASTROINTESTINAL DRUG ABSORPTION	12/01/2004

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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